Exhibit 4

Express Mail No. EV 809 954 664 US

Contact Dermatitis, 1997, 36, 147–149
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CONTACT DERMATITIS
ISSN 0105-1873

Skin reactions to hydroxyzine

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Sensitivity to histamine H1-antagonists has mainly been observed with phenothiazine and ethylenediamine, and is very rare with hydroxyzine. We report 3 cases of sensitization to hydroxyzine, which was prescribed to treat urticaria and atopic dermatitis. A generalized maculopapular eruption appeared shortly after taking the drug. Patch tests with Atarax® tablet were positive +++, and ++ or +++ with different dilutions of hydroxyzine. Patch tests with ethylenediamine, piperazine and other antihistamines were negative; therefore, there is no cross-allergy. We believe these rapid systemic reactions to hydroxyzine after the initial dose may have been due to prior systemic sensitivity to this drug, which cannot be used topically. Allergy to antihistamines must be considered when cutaneous lesions worsen on such therapy.

Key words: hydroxyzine; histamine H1-antagonists; antihistamine drug eruption; adverse drug reaction; lack of cross-sensitivity. © Munksgaard, 1997.

Accepted for publication 23 November 1996

Adverse drug reactions to histamine H1–antagonists are rare. This chemical family is divided into several groups ; phenothiazine and ethylenediamine subgroups are the main potential allergens (1). Allergy to hydroxyzine, which is close in structure to piperazine, has rarely been reported (2). We report 3 cases.

Patients and Methods

Patient no. 1

In December 1992, a 65–year-old woman was referred to our department with an adverse cutaneous drug reaction to Lariam® (mefloquine: Roche, Neuilly-Sur-Seine, France). To calm the pruritus, treatment with Atarax® tablets 100 mg/day (hydroxyzine: UCB Pharma, Nanterre, France) was introduced. At that time, we were surprised that, although Lariam® had been stopped the eruption healed so slowly. In January 1993, Atarax® was withdrawn. In April 1993, the patient developed urticaria which was treated with Atarax® 25 mg/day and Clarityne® tablets 10 mg/day. 12 h later, a generalised maculopapular eruption appeared. The eruption healed after discontinuance of Atarax® and Clarityne®. Urticaria was also cured. Patch testing was performed in January 1994 and June 1994.

Patient no. 2

For 20 years, a 36–year-old woman had eczema of the face and hands. She was atopic but she also had contact dermatitis from colophony, balsam of Peru, fragrance and oakmoss. Recurrences of eczema were treated with topical corticosteroids and several antihistamines, including Atarax®. In July 1995, she presented with an acute eczema of the face treated with Atarax® 25 mg/day and Noctran® (clorazepate dipotassique, acepromazine, aceprometazine: Menarini, Rungis, France). 3 days later, a generalized maculopapular eruption appeared. This eruption healed after discontinuation of Atarax® and Noctran®. Patch testing was performed in September 1995 and April 1996.

Patient no. 3

In December 1995, a 35–year-old woman was admitted at risk of premature labor. She was treated with Natisédine® (phenobarbital, passiflore: Procter & Gamble pharmaceuticals, Neuilly-sur-Seine, France), Pré-Par® (ritodrine: Solvay Pharma, Suresnes, France) and Salbumol® (salbutamol: Glaxo Wellcome, Paris, France) before delivery. She also took Maxilase-Bacitracine® tablets (alpha-amylase, bacitracin: Sanofi Winthrop, Gentilly, France) for a sore throat. 3 days later she presented with urticaria which was treated with Atarax® 25 mg/day and Polaramine® 2 mg/day (dexchlorpheniramine: Schering-Plough, Levallois-Perret, France). As soon as she started antihistamines, her urticaria worsened and became more pruriginous. 2 days later, she underwent a caesarian operation and other drugs were prescribed:

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Syntocinon® (oxytocin: Sandoz, Rueil-Malmaison, France), Pro-Dafalgan® (propacetamol: UPSA, Rueil-Malmaison, France), Zinnat® (cefuroxime: Glaxo Wellcome, Paris, France), Profénid® (ketoprofen: Specia, Paris, France), Fragmine® (dalteparin sodium: Pharmacia, Saint-Quentin-Yvelines, France) and Parlodel® (bromocriptine: Sandoz, Rueil-Malmaison, France). After the delivery, a morbilliform eruption appeared. 7 days later, the patient presented with a fever of 40°C, adenopathy and erythroderma. Multiple microbiologic cultures and viral serologies eliminated infectious disease. 5 days after the discontinuance of all drugs except Parlodel®, the cutaneous lesions cleared.

Skin testing

Using Finn Chambers (Epitest, Tuusula, Finland), the 3 patients were tested with the European standard series, their topical medicaments and systemic drugs. All drugs, including Atarax®, were tested with a crushed tablet diluted in water. Prick tests were also performed with Atarax® tablets. A few months later, other patch tests were performed with different dilutions (2%, 5%, 10% aq.) of hydroxyzine hydrochloride and all the other components of Atarax® tablets: macrogol 6000 (5% aq.), colloidal silica (5% aq.), povidone K30 (5% aq.), microcrystalline cellulose (5% aq.), magnesium stearate (5% aq.), eudragit E (20% pet.), lactose (20% aq.), talc (as is) and titanium dioxide (5% aq.). They were also patch tested with piperazine (1% pet.), ethylenediamine (1% pet.), and triethanolamine (2.5% pet.) marketed by Isotec (Saint Quentin, France) and 6 other histamine H1-antagonists: dexchlorpheniramine (Polaramine®), loratadine (Clarityne®), chlorpromazine (Phénergan®), mequitazine (Primalan®), terfenadine (Teldane®) and cetirizine (Zyrtec®). Reading was performed 3 days later according to international convention. 190 control subjects were tested with Atarax® tablets.

Results

All 3 patients gave positive patch tests (+++) with Atarax® tablet and with the different dilutions of hydroxyzine (+++ or ++) (Fig. 1). All the other components of Atarax® tablet, and also the prick tests with Atarax®, were negative. Piperazine, ethylenediamine, triethanolamine and the 6 other antihistamines were negative. Patient no. 2 had a positive patch test (+) to tomato. Patient no. 3 had doubtful reactions to Natisédine® and Zinnat®. The 190 control subjects had negative patch tests with Atarax® tablet.

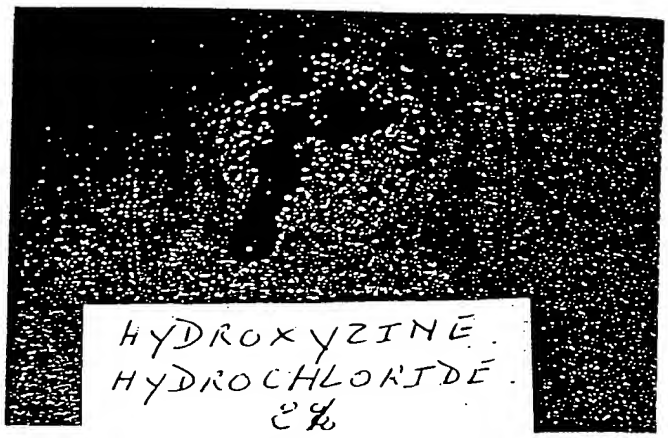

Fig. 1. Patient no. 3: positive patch test to hydroxyzine hydrochloride (2% aq.)

Discussion

Hydroxyzine is a 1st generation histamine H1–antagonist that is derived from piperazine. This drug also blocks muscarinic-cholinergic, α-adrenergic and 5-hydroxytryptaminergic receptors. It is an antiallergic drug but also a tranquillizer, a hypnotic and used as preoperative medication.

The 1st generation of histamine H1-antagonists is divided into 6 subgroups: alkylamine, ethanolamine, ethylenediamine, piperazine, piperadine and phenothiazine. They all have the basic structure of histamine modified by substitution on the imidazole ring. They have effects especially on H1-mediated reactions (3). Their side-effects are sedation, daytime drowsiness and neuroleptic effects. They also block other receptors : urinary retention, nasal stuffiness and blurring of vision are related to their anticholinergic properties (4). These adverse reactions have limited the use of the classical antihistamines. There are new 2nd generation H1-receptor antagonists that are more selective and less sedative. However, hydroxyzine is still widely used because of its availability in formulation for parenteral use, relatively high benefit-risk ratio and suitability for 1× daily administration.

Skin sensitization occurs with the use of ethylenediamine and phenothiazines (5–7), the latter also producing photosensitivity (8–10). Recently, skin reaction to terfenadine has been reported (11). Like all antihistamines, hydroxyzine can induce cutaneous sensitization, though very few cases have been reported (2, 4). The generalized polymorphous rash that our patients had after taking hydroxyzine was very difficult to differentiate from the initial one. All 3 patients initially presented with urticaria (nos. 1, 3) or eczema (no. 2), which necessitated the prescription of drugs including

Atarax®. Secondarily, another iatrogenic cutaneous eruption appeared; Atarax®, but also other drugs, could have been involved in the genesis of this 2nd eruption. Allergy to hydroxyzine was demonstrated by the positivity of patch tests (12). These tests seem reliable because there was no false positive reaction in 190 control subjects.

Topical and systemic use of antihistamines can both induce skin sensitization. In our patients it was probably systemic sensitization because topical hydroxyzine does not exist. Besides, 2 of them had taken Atarax® a few months before. Topical use of H1-antagonists often produces local sensitization. Cross-reactions between ethylenediamine, present in some creams, and the ethylenediamine H1-antagonists aminophylline and piperazine have been reported (13, 14). Fisher (1) has shown that there is cross-allergy between different groups of antihistamines because of their structural similarities. Therefore, patients sensitized to hydroxyzine, which is a piperazine antihistamine, are also sensitized to ethylenediamine. In contrast to other published cases, our patients had positive patch tests to hydroxyzine but negative tests with piperazine, ethanolamine and ethylenediamine. Many 1st and 2nd generation antihistamines' tests are negative, including cetirizine, which differs from hydroxyzine by an acid function. Allergy to antihistamines must be considered when cutaneous lesions worsen on antihistamine therapy.

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